

A DRUG NAME: FLUOROURACIL**SYNONYM(S)**: 5-Fluorouracil, 5FU**COMMON TRADE NAME(S)**: Fluorouracil Injection USP (Mayne Pharma)(Valeant Canada), Efudex® Cream (Valeant Canada), Fluoroplex® Cream (Allegan)**B MECHANISM OF ACTION AND PHARMACOKINETICS**

Fluorouracil was developed in 1957 based on the observation that tumour cells utilized the base pair uracil for DNA synthesis more efficiently than did normal cells of the intestinal mucosa. It is a fluorinated pyrimidine that is metabolized intracellularly to its active form, fluorouridine monophosphate (FdUMP). The active form inhibits DNA synthesis by inhibiting thymidylate synthetase and the normal production of thymidine. Effects on RNA (incorporation into RNA and RNA inhibition) occur especially with bolus administration. Fluorouracil is cell cycle phase-specific (S-phase).

Oral Absorption	28-100%
Distribution	Into all body water by passive diffusion, crosses placenta, high and persistent levels in malignant effusions
	Cross blood brain barrier? Yes
	Vd 0.25 L/kg, 8.84 L/m ² , 12-89% of body water
	PPB 8-12%
Metabolism	Activated in target cells, catabolized in liver, most of dose (80%) eliminated by liver
	Active metabolite(s) Yes
	Inactive metabolite(s) Yes
Excretion	60-80% excreted as respiratory CO ₂ , 2-3% by biliary system
	Urine 20% as intact drug within 6 hours
	t _{1/2} 10-20 minutes
	Cl 0.6-2.3 L/min, 16 mL/min/kg, women 155 L/h/m ² , men 179 L/h/m ²

C INDICATIONS AND STATUS

- * Breast cancer (adjuvant/palliative)
 - * Colorectal cancer (adjuvant/palliative)
 - * Gastric cancer
 - * Pancreatic cancer
 - * Cancer of urinary bladder
 - * Cancer of the prostate
 - * Cancer of the head and neck
 - * Cancer of the ovary
 - * Superficial basal cell carcinoma (topical)
 - * Premalignant keratoses (topical)
- * *Health Canada approved indication*
- Other uses include:
Endometrial cancer
Hepatic cancer

D ADVERSE EFFECTS

ORGAN SITE	SIDE EFFECT	ONSET	
Cardiovascular	Asymptomatic ECG changes (67%)	I	
	Myocardial ischemia (2-3%)	I	
Central nervous system	Acute cerebellar syndrome (< 1%)		E D
	Photophobia		
	Acute encephalopathy/euphoria(rare)		E D
Dermatologic	Alopecia (mild)		E
	Hyperpigmentation (over veins used)		E
	Rash (extremities, sometimes on trunk)		E
	Nail changes		E
	Photosensitivity, dry skin		E
	Palmar-plantar erythrodysesthesia (hand-foot syndrome)		E
	Radiation recall reaction (rare)	I	
	Erythema, necrosis (topical application)	I	E
Extravasation hazard (refer to Appendix 2)	None		

D	ADVERSE EFFECTS (continued)			
	ORGAN SITE	SIDE EFFECT	ONSET	
Gastrointestinal		Mild nausea and vomiting	I	
		<u>Stomatitis, esophagitis</u>	E	
		GI Bleeding (rare)		
		Anorexia	E	
		<u>Diarrhea</u>	E	
Hematologic		<u>Myelosuppression (very common)</u> Nadir 7-14 days, recovery 22-24 days	E	
		Immunosuppression	E	
		Hemolytic-uremic syndrome (with mitomycin)		
		Megaloblastosis	E	
Hypersensitivity	Type I (anaphylactoid, rare)	I		
Injection site	Chemical phlebitis	I		
Ocular		Excessive lacrimation; Tear duct fibrosis	I	D
		Conjunctivitis	I	
		Abnormal convergence/divergence	E	

Dose-limiting side effects are underlined.

I = immediate (onset in hours to days); E = early (days to weeks);
D = delayed (weeks to months); L = late (months to years)

Following longer IV infusions, **stomatitis and diarrhea** occur most commonly. Diarrhea may be profuse and life threatening following administration of leucovorin with fluorouracil. **Leukopenia** is the usual dose-limiting toxicity after IV bolus administration.

Patients with dihydropyrimidine dehydrogenase deficiency are at risk of severe life threatening toxicity with fluorouracil. While severe deficiency is rare, 3-4% of the population has some degree of DPD deficiency.

Excessive lacrimation occurs frequently. Transient blurring of vision, eye irritation and excessive **nasal discharge** have also been reported. The onset of eye symptoms may occur at any time during treatment. Fluorouracil has been demonstrated in tear fluid causing acute and chronic conjunctivitis that can lead to tear duct fibrosis.

D ADVERSE EFFECTS (continued)

Acute cerebellar syndrome is manifested as ataxia of the trunk or extremities, disturbance of gait and speech, coarse nystagmus and dizziness. The ataxia syndrome is related to peak plasma levels of the drug rather than to cumulative dose, and is therefore more common with bolus doses than with infusions.

Palmar-plantar erythrodysesthesia or hand-foot syndrome has been noted with protracted and high dose continuous infusion (23-82%). The syndrome begins with dysesthesias of the palms and soles that progress to pain and tenderness. There is associated symmetrical swelling and erythema of the hand and foot. Treatment with 50 or 150 mg of pyridoxine daily has been associated with reversal of the syndrome. The syndrome resolves with cessation of drug infusion.

Fluorouracil has the potential to enhance radiation injury to tissues. While often called **radiation recall reactions**, the timing of the radiation may be before, concurrent with or even after the administration of the fluorouracil. Recurrent injury to a previously radiated site may occur weeks to months following radiation.

Hemolytic uremic syndrome has been reported when used in combination with mitomycin C.

When applied to a lesion, the following occurs: erythema, usually followed by vesiculation, erosion, ulceration, necrosis and epithelization. The lower frequency and intensity of activity in adjacent normal skin indicates a selective cytotoxic property. The cream is preferably applied with a nonmetal applicator or glove. If applied with the fingertips, the hands should be washed immediately afterwards. Apply with care near the eyes, mouth and nose. An occlusive dressing is not essential, and may increase the incidence of inflammatory reactions in adjacent normal skin. Therapy is usually continued to reach the erosion, necrosis and ulceration stage (2-4 weeks), after which healing occurs over 4-8 weeks. The most frequent local reactions are pain, pruritis, hyperpigmentation and burning at the application site. Avoid prolonged exposure to ultraviolet light while under treatment as the intensity of the reaction may be increased.

E DOSING

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy, or in patients with poor nutritional or performance status. Fluorouracil should be held immediately with rapidly falling counts, severe vomiting, diarrhea or stomatitis; after recovery, dose modifications should be considered.

IV bolus: q4w: 250-500 mg/m² day x 5 days
q4w: 400-500 mg/m² days 1 & 8

IV infusion: q1w: 2.6 g/m² over 24 hours
q3-4w: 400-1000 mg/m²/day x 4-10 days as continuous infusion

Dosage with myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to [Appendix 6](#) "Dosage Modification for Myelosuppression"

Dosage with renal impairment: no adjustment required, although reduction may be considered with severe renal insufficiency

Dosage with hepatic impairment: omit if bilirubin > 4 x ULN (upper limit of normal)

Topical: daily: x 1-4 weeks. Glove or non-metal applicator preferred. If fingertips used, wash hands immediately. Stop when erosion evident, usually 2-4 weeks. Allow 1-2 months for healing. Total area treated at one time should not exceed 500 cm² (23x23 cm). Larger areas should be treated one section at a time.

F ADMINISTRATION GUIDELINES (see [Appendix 3a](#))

- Slow push through sidearm of free flowing IV (5% Dextrose, Normal Saline or 2/3.1/3)
- May be given by direct IV push, followed by a Normal Saline flush, if no IV line has been set up
- May be mixed in 50ml minibag (NS or DSW); infuse over 15 min.

FLUOROURACIL INFUSION:

- Continuous infusion using CADD infusion pump, or similar device
- Infuse through central venous access device, if available
- Infuse through patent peripheral venous catheter, if infusion for only 3-5 days; Inspect peripheral infusion sites daily and replace if evidence of irritation or extravasation
- **PROTECT FROM LIGHT**
- Incompatible with doxorubicin, epirubicin, diazepam, methotrexate and cytarabine; line must be flushed prior to administration of these agents

G SPECIAL PRECAUTIONS

Fluorouracil is **contraindicated** in patients with poor nutritional state, depressed bone marrow function (prior pelvic irradiation / marrow infiltration), or potentially serious infections and in patients with known hypersensitivity to the drug.

Fluorouracil is **teratogenic**, and has potential **mutagenic and carcinogenic** effects and should not be used in **pregnancy**. Adequate contraception should be used. Its effects on **fertility** have not been established. **Breast feeding** is not recommended due to the potential secretion into breast milk.

H INTERACTIONS

AGENT	EFFECT	MECHANISM	MANAGEMENT
Allopurinol	decreased toxicity of fluorouracil	possibly inhibition of thymidine phosphorylase	caution
Mitomycin	increased incidence of hemolytic-uremic syndrome	unknown	
Cimetidine	increased serum concentrations of fluorouracil	appears to interfere with fluorouracil metabolism	observe for increased toxicity of fluorouracil
Leucovorin	increased cytotoxic and toxic effects of fluorouracil	Leucovorin stabilizes the bond to thymidylate synthetase	some protocols are designed to take advantage of this effect; monitor toxicity closely

H INTERACTIONS (continued)

AGENT	EFFECT	MECHANISM	MANAGEMENT
Metronidazole	enhanced toxicity of fluorouracil	decreased clearance of fluorouracil	monitor for increased toxicity of fluorouracil
Thiazide diuretics	increased myelosuppression	decreased renal excretion of fluorouracil	consider an alternative antihypertensive
Warfarin	increased effect of warfarin	reduced warfarin clearance	monitor closely

I RECOMMENDED CLINICAL MONITORING**Recommended Clinical Monitoring****Suggested Clinical Monitoring**

Regular clinical assessment and grading of stomatitis, diarrhea, local site toxicity, skin effects (rash or hand-foot-syndrome)

Regular CBC before repeat doses

Baseline liver & renal function tests

J REFERENCES

Cancer Drug Manual (the Manual), 1994, British Columbia Cancer Agency (BCCA)

Product Monograph: Fluorouracil. Mayne Pharma. 2007